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Re: Docket No. 99P-5215/CP1

Dear Counsel:

This letter responds to your petition dated December 2, 1999. You request that the FDA revoke the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients (pediatric rule) (see 63 FR 66631; Dec. 2, 1998). FDA denies your petition for the reasons set forth below.

1. The pediatric rule does not conflict with pediatric exclusivity.

You argue that FDA should revoke the pediatric rule because it conflicts with the pediatric exclusivity program created by section 111 of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act)(section 505A of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355a)). Although pediatric exclusivity provides a substantial incentive for some sponsors to conduct pediatric studies, the Agency nonetheless believes that the pediatric rule is necessary to provide adequate labeling for the wide range of products that are being used in children without necessary information on pediatric dosing, safety, and effectiveness. Certain limitations on the scope and effect of pediatric exclusivity are likely to leave significant gaps in pediatric labeling. For example, because pediatric exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and/or the Orphan Drug Act, it provides no incentive to conduct studies on certain categories of products, including most antibiotics, biologics, and off-patent products.

In addition, the voluntary nature of the pediatric exclusivity incentive is likely to leave many drugs, age groups, and indications unstudied. Given limited resources to conduct pediatric studies, manufacturers are likely to conduct pediatric studies on those drugs for which the incentives are most valuable (i.e., on drugs with the largest sales). This will leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. For similar reasons, manufacturers are less likely to seek pediatric exclusivity by conducting studies on drugs that require studies in neonates, infants, or young children. The youngest pediatric

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populations are more difficult to study and may require pediatric formulations, making pediatric studies of these groups more expensive, thereby reducing the value of pediatric exclusivity and making it less likely they will be studied. Thus, where there is a great medical need for data on drugs with relatively small markets or for studies on neonates, infants, or young children, it may be necessary to require the collection of such data, rather than rely only on incentives to protect the public health.

Finally, manufacturers are eligible for pediatric exclusivity when they submit a study to FDA that is consistent with FDA's written request for such a study, not when they label their products for pediatric use. The sponsor is not required to obtain approval of labeling which incorporates pediatric study results, and thus make the information available for the marketed product. Therefore, pediatric exclusivity, while generating potentially valuable pediatric study results, provides no guarantee that the studies conducted will result in improved pediatric labeling that benefits patients and practitioners.

For these reasons, FDA believes that there remains an important need for the pediatric rule, despite the pediatric exclusivity provisions of the Modernization Act. FDA has concluded, however, that for already-marketed drugs eligible for pediatric exclusivity, the availability of pediatric exclusivity may diminish the need to exercise the Agency's authority to require pediatric studies. Under the rule, FDA has the discretion to determine whether to require studies of marketed drugs (see 21 CFR 201.23). FDA believes that, in exercising its discretion under section 201.23, it is appropriate to determine whether manufacturers will undertake the needed studies voluntarily. FDA is therefore allowing an adequate opportunity for manufacturers voluntarily to submit studies for already-marketed drugs. FDA has not yet required any pediatric studies to be submitted on already-marketed drugs. If there remain marketed drugs for which studies are needed and the compelling circumstances described in the rule are met, the Agency will consider exercising its authority to require studies. With respect to marketed drugs and biologics that are not eligible for pediatric exclusivity, FDA intends to exercise its authority to require studies in the circumstances described in the regulation. FDA intends to reserve its authority to require studies of marketed drugs and biologics for situations in which the compelling circumstances described in 21 CFR 201.23(b) are present (see 63 FR 66631 at 66633-34).

As you correctly note in your petition, the pediatric exclusivity provisions of the Modernization Act require the Secretary to report to Congress by January 1, 2001, on a number of issues related to the exclusivity. The report must address the effectiveness of the program, the adequacy of the exclusivity incentive, the economic impact of the exclusivity on taxpayers and consumers, and any modifications that would be appropriate. FDA intends to include in this report its observations regarding the limitations of the current pediatric exclusivity program in ensuring that drugs of importance to children are studied and adequately labeled for use in pediatric populations, and to propose certain modifications to better accomplish that goal.

2. Although certain costs are associated with the pediatric rule, FDA believes that the rule is necessary to ensure the safe and appropriate use of drugs and biologics in children.

You argue that the pediatric rule increases the cost of pharmaceuticals. FDA prepared a complete economic analysis that describes the estimated costs of complying with the pediatric rule (see 63 FR 66631 at 66660-67; 62 FR 43900 at 43909-13). Although FDA recognizes that there will be certain costs associated with complying with the pediatric rule, the Agency believes these costs are necessary to ensure the safe and appropriate use of drugs and biologics in children. As discussed in detail in sections 5 and 7 of this citizen petition response, the absence of pediatric labeling information poses significant risks for children (see also 63 FR 66631 at 66632; 62 FR 43900 at 43900-01), and these risks carry costs in both economic and human terms.

The pediatric exclusivity program also carries with it increased costs to taxpayers and consumers caused by the 6-month delay in entry into the market of lower cost generic drug products. The nature and extent of these costs will be discussed in the Secretary's report to Congress. Despite the fact that developing adequate pediatric labeling will doubtless entail certain costs to pharmaceutical companies, taxpayers, and the public, it is the Agency's view that providing pediatric patients access to safe and effective drug products is a compelling public health goal.

3. The pediatric rule will not result in delays in approval of drugs for use in adult populations.

You assert that the pediatric rule will delay the introduction of new drugs and hamper pharmaceutical innovation, in contravention of provisions of the Modernization Act directed at accelerating drug approvals. This is not correct. The specific provisions of the Modernization Act directed at expediting the drug approval process apply equally to the review of drugs used for the treatment of children. In addition, the pediatric rule specifically provides that it will not delay introduction of new drugs ready for approval in adults pending receipt of pediatric studies, but instead will defer requiring receipt of those studies (see 21 CFR 314.55(b)). The pediatric rule includes provisions for early consultation and meetings on pediatric studies, deferrals, and waivers, so that the conduct of pediatric studies need not delay the approval of drugs for use in adult populations (21 CFR 312.47; 21 CFR 312.82). Moreover, the implementation process for the pediatric exclusivity program has provided FDA and the pharmaceutical industry with valuable experience and insight into the type and extent of information needed to adequately label drugs for use in children, and the design and conduct of pediatric trials. This experience will assist FDA and industry in implementing the pediatric rule. To the extent that conduct of pediatric studies poses a new challenge to the pharmaceutical industry, they have shown through their participation in the pediatric exclusivity process that they have the resources and skill to undertake the task in a timely manner.

4. FDA has the legal authority to issue the pediatric rule.

You argue that FDA's issuance of the pediatric rule is an illegal assertion of authority. FDA disagrees. The Agency has ample authority to require accurate pediatric labeling on drugs for use in pediatric patients for approved indications. Sections 502(a), 502(f), and 505(d)(7) of the Act, and 21 CFR 201.5 require products to bear adequate directions for use and prohibit false or misleading labeling. Section 351 of the Public Health Service Act requires biological products to be safe, pure, and potent. Section 201(n) of the Act defines as misleading labeling that fails to reveal material facts related to consequences of the customary or usual use of a drug. Sections 201(p), 301(a) and (d) (21 U.S.C. 321(p), and 331(a) and (d)), and 505(a) of the Act subject a drug, as defined in section 201(g) of the Act, to enforcement action if it is not generally recognized as safe and effective or approved for the conditions prescribed, recommended, or suggested in the labeling. Section 502(j) of the Act prohibits the marketing of drugs that are dangerous to health when used in the manner suggested in their labeling. Sections 505(i) and 505(k) of the Act authorize FDA to impose conditions on the investigation of new drugs, including conditions related to the ethics of an investigation, and to require postmarketing reports. Section 701(a) of the Act authorizes FDA to issue regulations for the efficient enforcement of the Act. Consonant with the Supreme Court's determination that the language of the Act should not be read restrictively, but in a manner consistent with the Act's purpose of protecting the public health, a regulation issued under section 701(a) of the Act will be sustained so long as it is reasonably related to the purposes of the Act (*United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240, 246 (2nd Cir. 1977)).

This rule is not the Agency's first assertion of legal authority to require pediatric studies. FDA notes that it previously stated this position in 1994, in the context of seeking submission of data adequate for pediatric labeling from published studies (see 59 FR 64240 at 64243).

FDA has authority under section 302 of the Act and under the Public Health Service Act to seek an injunction requiring studies of certain marketed drugs on the grounds that the absence of pediatric safety and effectiveness information in the labeling renders the product misbranded or an unapproved new drug. The Act also authorizes seizures of misbranded or unapproved drugs under section 304. Misbranding drugs and introducing unapproved new drugs into interstate commerce are prohibited acts under sections 301(a), (d), and (k) of the Act. FDA issued the pediatric rule under authority derived from all of these provisions of the Act.

FDA also believes that the reference in section 505A of the Act and its legislative history to pediatric studies required by FDA demonstrates that Congress agrees the Agency has the authority to require pediatric studies. This provision was enacted after FDA proposed the pediatric rule, and Congress could easily have asserted at the time that the pediatric exclusivity process was the only acceptable mechanism whereby FDA could obtain pediatric study data. It did not.

For these reasons, and because of the factual basis on which the rule is premised, FDA has legal authority to require studies on the use of drugs to treat approved indications in pediatric patients.

5. **The pediatric rule does not represent an unnecessary intrusion into manufacturers' decisional prerogatives concerning intended purchasers.**

You argue that the pediatric rule represents an unnecessary intrusion into manufacturers' decisional prerogatives concerning intended purchasers. FDA disagrees. As discussed in detail below, FDA may consider the actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer (section 201.128). Further, the pediatric rule is necessary because the absence of pediatric labeling information poses significant risks for children. Inadequate dosing information exposes pediatric patients to potentially ineffective doses, potential overdosing, and the risk of adverse reactions that could be avoided with an appropriate pediatric dose. The lack of pediatric safety information in product labeling exposes pediatric patients to the risk of age-specific adverse reactions that are not expected in adults. The absence of pediatric testing and labeling may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. If younger pediatric populations cannot take the adult formulation, failure to develop a pediatric formulation of a drug or biological product may also deny pediatric patients access to important new therapies, or may require pediatric patients to take the drug in extemporaneous formulations that may be poorly or inconsistently bioavailable. FDA believes that pediatric patients should receive the same standard of care based upon adequate safety and effectiveness information for pharmaceuticals as adult patients treated with the same drugs for the same labeled indications. This requires developing pediatric use information and labeling products appropriately.

6. **Sponsors have not submitted adequate pediatric labeling information under FDA's voluntary programs.**

FDA used a number of alternative approaches to obtain pediatric labeling before it issued the pediatric rule requiring pediatric studies. These methods proved inadequate. FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research implemented a "Pediatric Plan" designed to focus attention on, and encourage voluntary development of, pediatric data, both during the drug development process and after marketing. In the *Federal Register* of December 13, 1994 (59 FR 64240) (the 1994 rule), FDA issued a regulation requiring manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support additional pediatric use information in the drug's labeling. Under the 1994 rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application to FDA seeking approval of the labeling change. Although the preamble to the 1994 rule

recognizes FDA's authority to require drug and biological product manufacturers to conduct pediatric studies on a case-by-case basis, the rule did not impose a general requirement that manufacturers carry out studies when existing information is not sufficient to support pediatric use information. Instead, if there was insufficient information to support a pediatric indication or pediatric use statement, the rule required the manufacturer to include in the product's labeling the statement: "Safety and effectiveness in pediatric patients have not been established."

The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products. Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information. Over half of the total supplements submitted simply requested the addition of the statement "Safety and effectiveness in pediatric patients have not been established." Others requested minor wording changes or submitted disorganized, unanalyzed collections of possibly relevant data. The Agency has projected that, if approved, approximately 15 percent (about 65) of the supplements submitted in response to the 1994 rule would provide adequate pediatric information for relevant pediatric age groups, and another 8 percent (approximately 35) would provide adequate pediatric information for some but not all relevant age groups.

The absence of adequate pediatric use information is a problem for new drug and biological products as well as for marketed products. In developing the pediatric rule, the Agency relied upon data from 1988 through the 1990s that showed that the percentage of new products entering the marketplace with adequate pediatric safety and effectiveness information has not increased in the last decade. For example, FDA compared the number of new molecular entities (NMEs) approved in 1991 and 1996 with potential usefulness in pediatric patients and looked at the adequacy of pediatric labeling for those drugs. Fifty-six percent (9/17) of the NMEs approved in 1991 with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. In 1996, only 37 percent (15/40) of the NMEs with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. For both 1991 and 1996, those drugs counted as having pediatric labeling may not have been studied in all age groups in which the drug was potentially useful. In 1997, 39 NMEs were approved. Twenty-seven had potential usefulness in pediatric patients, and 33 percent of these (9/27) had some pediatric labeling at the time of approval. These figures reflect both studies that resulted in positive labeling (i.e., safety and dosing information), and studies that resulted in warnings against pediatric use. They do not reflect studies that failed to provide any useful information about pediatric use or studies that were completed but the sponsor failed to seek a change in its pediatric use labeling.

Moreover, even commitments by specific sponsors to conduct postapproval pediatric studies on their recently approved drugs have not generated substantial information. The manufacturers of an additional 7 of the 1991 drugs and 17 of the 1996 drugs promised to conduct pediatric studies after approval. Between 1991 and 1996, there were 71 phase 4 studies promised for products that would be used in children. As of 1997, only 11 of the 71 studies had been completed.

Postapproval studies were requested or promised for an additional six of the drugs approved in 1997. It is uncertain how many of the commitments made for postapproval studies of the 1997 drugs will result in pediatric labeling (Exhibit 1).

These data indicate that voluntary efforts had not, by 1997, substantially increased the number of products entering the marketplace with adequate pediatric labeling. FDA therefore concluded that certain requirements were necessary to ensure the safety and effectiveness of drug and biological products for pediatric patients, and therefore proposed and finalized the pediatric rule.

7. FDA has the authority to require a drug or biologic to be studied for use in the populations for which it is reasonably expected to be used for the approved indication.

FDA has the authority to require a drug or biologic to be studied in a population that is expected to use the product for the claimed indication. As is expressly stated in the preambles to both the proposed and the final rule, the rule requires the assessment of safety and effectiveness for pediatric patients only for the indication for which the sponsor either seeks, or has already obtained, approval. It does not require the manufacturer to study the drug for other unapproved indications, even if the drug may be widely used for those indications. Contrary to the assertion in your petition, the rule does not interfere with a physician's ability to prescribe drugs and biological products for use by pediatric patients for unapproved indications (62 FR at 43903; 63 FR at 66634).

The Agency has repeatedly stated that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given the product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409). The Agency has also previously asserted its authority to require studies in pediatric patients and in other subpopulations for both not-yet-approved products and marketed products. In the preamble to the 1994 rule, FDA made the following statement:

> If FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric populations, and the drug sponsor has not submitted any pediatric use information, then the Agency may require that the sponsor develop and/or submit pediatric use information.
>
> If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as an unapproved new drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262.)

(59 FR 64240 at 64248; see also 58 FR 39406 at 39409).

The Act and implementing regulations require drugs to be adequately labeled for their intended uses (see section 502(f) of the Act and 21 CFR 201.5). The "intended uses" encompass more than the uses explicitly included in the manufacturer's proposed labeling (see 21 CFR 201.128). In determining the intended uses of a drug for which it must be adequately labeled, FDA may consider both the uses for which it is expressly labeled and those for which the drug is commonly used (section 201.5). FDA may also consider the actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer (section 201.128). Section 201(n) of the Act defines labeling as misleading if it fails to include material facts about the consequences of "use of the [drug] * * * under such conditions of use as are customary or usual." Section 505(d) of the Act authorizes FDA to require evidence establishing the safety and effectiveness of uses "suggested" by the manufacturer's labeling as well as those expressly recommended in the labeling of a new drug. Thus, the Agency has authority to require a manufacturer to establish the safety and effectiveness of, and adequately label its product for, use in a subpopulation for which the product is not labeled if that use is common or is suggested in the labeling.

There is extensive evidence that drugs and biologics indicated for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in pediatric patients. FDA may therefore consider pediatric use to be "customary or usual" or "commonly used" where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. FDA may also consider pediatric use to be "suggested" in a drug's labeling even where such use is not expressly recommended or is even disclaimed. The medical community generally expects that drugs and biological products will behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, for example, differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease equally affecting men, women, and children, and is not contraindicated in women or pediatric patients, the product is likely to be widely prescribed for all three subgroups, even if studied only in, or labeled only for, men.

Pediatricians often have no choice but to use these products in pediatric patients. A drug product that provides a meaningful therapeutic benefit, either because it represents a significant improvement in therapy or because it is a necessary therapeutic option, can reasonably be expected to be routinely used in the treatment of pediatric patients. Under the rule, the decision that a product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients is made on a case-by-case basis, depending upon such factors as the number of pediatric patients affected by the disease for which the product is indicated, the availability and adequacy of other therapeutic options to treat pediatric patients for the disease, and whether similar products (e.g., products in the same drug class) have been widely used in pediatric patients.

Finally, FDA emphasizes that this rule applies only if a product is expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer. The record before the Agency documents widespread evidence of actual use of many products in the pediatric population for indications labeled for adults. This record supports FDA's conclusion that it has authority to require pediatric studies of drugs and biologics that have or are expected to have clinically significant use among pediatric patients for the claimed indications. The Agency emphasizes again that the pediatric rule does not require studies of the pediatric use of drugs for indications for which the drug product is not labeled or seeking approval.

8. FDA is actively addressing ethical issues involving pediatric clinical trials; these issues generally will be the same for studies conducted pursuant to the pediatric rule and for studies earning pediatric exclusivity.

Your petition asserts that the pediatric rule raises particular ethical problems related to the conduct of pediatric studies because it requires certain pediatric information. You further assert that the Modernization Act's pediatric exclusivity program minimizes these ethical issues. The Agency disagrees. First, there is no doubt that at whatever stage in drug development pediatric studies are conducted, they pose special ethical issues. These issues have been the subject of intense discussion and concern at the Agency, and among other experts in medicine and ethics (see, e.g., Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee Meetings, Nov. 15-16, 1999 (discussing assent, consent, benefit, studies in healthy children, compensation, and risk); and Sept. 11, 2000 (discussing placebo controlled trials)).[1] Second, although the presumption in the pediatric rule is that drugs will be required to have adequate pediatric labeling, the Agency will not require studies that violate ethical standards. Throughout the preamble to the rule, and embodied in the regulations themselves, are concerns that pediatric studies of drugs be conducted at the appropriate stage of drug development. The provisions for deferral and waiver of pediatric studies are intended to ensure that drugs are studied, if at all, at the stage of drug development that best balances the potential benefit to the pediatric population against concerns regarding the safety and effectiveness of the drug. The Agency will consider the seriousness of the disease or condition the drug is intended to treat, the available alternative treatments, and the data available on the safe and effective use of the drug in adults. In some cases it may be appropriate to begin pediatric trials before the drug is approved in adults; in other cases pediatric trials may not be appropriate until the drug is approved for use in adults and additional data on safety and effectiveness is available. Such decisions will be made on a case-by-case basis during the meeting process described at 21 CFR 312.47 and 312.82. Deferral and waiver decisions will be made based on the considerations described in 21 CFR 314.55. Please refer to the Agency's responses to comments on deferred studies, waivers, and ethical

[1] Recently, Congress passed legislation directing FDA to require pediatric research be conducted in compliance with 45 CFR part 46 subpart D, and directing the Secretary of Health and Human Services to conduct a review of these regulations (see sections 1003 and 2701 of the Children's Health Act of 2000, Public Law 106-310 (Oct. 17, 2000)). In response to recommendations from the November 15-16, 1999 Pediatric Advisory Committee, FDA had already begun the process of adopting the subpart D protections prior to passage of this legislation

considerations in the final rule for additional information on this issue (see 63 FR at 66642-48, 66654-55).

Finally, the Modernization Act provides pediatric exclusivity for studies not just on already approved and marketed drugs, but also on unapproved drugs, for which safety and effectiveness in adults has not yet been established (section 505A(a) of the Act). When the Agency develops a written request for studies under that section, it considers the same ethical issues that arise in applying the pediatric study requirements of the rule.

9. The issue of how the pediatric rule applies to suitability petitions is a small part of the pediatric rule and is under separate consideration.

Finally, you requested that FDA consolidate a suitability petition submitted by Faulding Pharamaceutical (Docket No. 99P-2252) with your petition. FDA responded to Faulding's petition on April 18, 2000 (Exhibit 2). FDA notes that the issue of how the pediatric rule applies to suitability petitions is under further Agency consideration as FDA works to reply to the citizen petition submitted in Docket No. 99P-4612. That petition requests that FDA continue to review and approve suitability petitions seeking a change in strength, dosage form, active ingredient, or route of administration, without applying the regulatory requirement that applications for changes in dosage form, active ingredient, or route of administration contain a pediatric assessment (see 21 CFR 314.55). FDA is working to resolve the complex issues associated with this petition request. However, even if FDA were to determine that the pediatric rule should not apply to suitability petitions, FDA would not invalidate the entire pediatric rule.

For the foregoing reasons, your petition is denied.

Sincerely yours,

William K. Hubbard
Senior Associate Commissioner for Policy,
Planning, and Legislation

Enclosures